(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 413 528 A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90308828.4

(51) Int. Cl.5: A61K 7/48, A61K 31/19

(22) Date of filing: 10.08.90

(30) Priority: 15.08.89 US 393749

(43) Date of publication of application:
20.02.91 Bulletin 91/08

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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(54) Amphoteric compositions and polymeric forms of alpha hydroxyacids, and their therapeutic use.

(57) Preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxyacids, alpha ketoacids, related compounds or polymeric forms of hydroxyacids is disclosed. The cosmetic conditions and the dermatologic disorders in which the amphoteric compositions and the polymeric compounds may be useful include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, kyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging, and skin requiring cleansers.

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AMPHOTERIC COMPOSITIONS AND POLYMERIC FORMS OF ALPHA HYDROXYACIDS, AND THEIR THERAPEUTIC USE

This invention relates generally to therapeutic treatment as well as preventive measures for cosmetic conditions and dermatologic disorders by topical administration of amphoteric compositions or polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds. We initially discovered that alpha hydroxy or keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne and warts.

We have now discovered that amphoteric compositions and polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds on topical administration are therapeutically effective for various cosmetic conditions and dermatologic disorders.

In order prior U.S. Patent No. 3,879,537 entitled "Treatment of Ichthyosiform Dermatoses" we described and claimed the use of certain alpha hydroxyacids, alpha ketoacids and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans. In our U.S. Patent No. 3,920,835 entitled "Treatment of Disturbed Keratinization" we described and claimed the use of these alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

In our prior U.S. Patent No. 4,105,783 entitled "Treatment of Dry Skin" we described and claimed th use of alpha hydroxyacids, alpha ketoacids and their derivatives for topical treatment of dry skin. In our recent U.S. Patent No. 4,246,261 entitled "Additives Enhancing Topical Corticosteroid Action" we described and claimed that alpha hydroxyacids, alpha ketoacids and their derivatives, could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis and other inflammatory skin conditions.

In our more recent U.S. Patent No. 4,363,815 entitled "Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions" we described and claimed that alpha hydroxyacids and alpha ketoacids related to or originating from amino acids, whether or not found in proteins, were effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier's disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus, warts and herpes.

In our most recent patent application Serial No. 945,680 filed December 23, 1986 and entitled "Additives Enhancing Topical Actions of Therapeutic Agents" we described and claimed that incorporation of an alpha hydroxyacid or related compound can substantially enhance therapeutic actions of cosmetic and pharmaceutical agents.

There is no doubt that alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically ffective for topical treatment of various cosmetic conditions and dermatologic disorders including dry skin, acne, dandruff, keratoses, age spots, wrinkles and disturbed keratinization. However, the compositions containing these acids may irritate human skin on repeated topical applications due to lower pH of th formulations. The irritation may range from a sensation of tingling, itching and burning to clinical signs of redness and peeling. Causes for such irritation may arise from the following:

Upper layers of normal skin have a pH of 4.2 to 5.6, but the compositions containing most alpha hydroxyacids or alpha ketoacids have pH values of less than 3.0. For example, a topical formulation containing 7.6% (1 M) glycolic acid has a pH of 1.9, and a composition containing 9% (1 M) lactic acid has the same pH of 1.9. These compositions of lower pH on repeated topical applications can cause a drastic pH decrease in the stratum corneum of human skin, and provoke disturbances in intercorneocyte bondings resulting in adverse skin reactions, especially to some individuals with sensitive skin.

Moreover, with today's state of the art it is still very difficult to formulate a lotion, cream or ointment emulsion which contains a free acid form of the alpha hydroxyacid, and which is physically stable as a commercial product for cosmetic or pharmaceutical use.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with a metallic alkali such as sodium hydroxide or potassium hydroxide the composition becomes therapeutically ineffective. Th reasons for such loss of therapeutic effects are believed to be as follows:

The intact skin of humans is a very effectiv barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by oral or oth r systematic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors; (a) bioavailability f the active ingredient in the topical preparation and (b) percutaneous absorption, penetration and distribution of

the active ingredient to the target site in the skin. For example, a topical preparation containing 5% salicylic acid is therapeutically effective as a keratolytic, but that containing 5% sodium salicylate is not an effectiv product. The reason for such difference is that salicylic acid is in bioavailable form and can pen trate th stratum corneum, but sodium salicylate is not in bioavailable form and cannot penetrate the stratum corneum of the skin.

In the case of alpha hydroxyacids, a topical preparation containing 5% glycolic acid is therapeutically effective for dry skin, but that containing 5% sodium glycollate is not effective. The same is true in cas of 5% lactic acid versus 5% sodium lactate. The reason for such difference is that both glycolic acid and lactic acid are in bioavailable forms and can readily penetrate the stratum corneum, but sodium glycollate and sodium lactate are not in bioavailable forms and cannot penetrate the stratum corneum of the skin.

When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormally with ammonium hydroxide or an organic base of smaller molecule the composition still shows some therapeutic effects for certain cosmetic conditions such as dry skin, but the composition has lost most of its potency for other dermatologic disorders such as wrinkles, keratoses, age spots and skin changes associated with aging.

It has now been discovered that amphoteric compositions containing alpha hydroxyacids, alpha ketoacids or related compounds, and also the compositions containing dimeric or polymeric forms of hydroxyacids overcome the aforementioned shortcomings and retain the therapeutic efficacies for cosm tic conditions and dermatologic disorders. The amphoteric composition contains in combination an amphot ric or pseudoamphoteric compound and at least one of the alpha hydroxyacids, alpha ketoacids or related compounds. Such amphoteric system has a suitable pH, and can release the active form of an alpha hydroxyacid or alpha ketoacid into the skin. The dimeric and polymeric forms of alpha, beta or other hydroxyacids in non-aqueous compositions have a more desired pH than that of the monomeric form of the hydroxyacids. The non-aqueous compositions can be formulated and induced to release the active form of hydroxyacids after the compositions have been topically applied to the skin. The cosmetic conditions and dermatologic disorders in humans and animals, in which the amphoteric compositions containing the dimeric or polymeric forms of hydroxyacids may be useful, include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, hyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging and as skin cleansers.

I. Amphoteric and Pseudoamphoteric Compositions

Amphoteric substances by definition should behave either as an acid or a base, and can be an organic or an inorganic compound. The molecule of an organic amphoteric compound should consist of at least one basic and one acidic group. The basic groups include, for example, amino, imino and guanido groups. Th acidic groups include, for example, carboxylic, phosphoric and sulfonic groups. Some examples of organic amphoteric compounds are amino acids, peptides, polypeptides, proteins, creatine, aminoaldonic acids, aminouronic acids, lauryl aminopropylglycine, aminoaldaric acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyalobiuronic acid, chondrosine and deacetylated chondroitin.

Inorganic amphoteric compounds are certain metallic oxides such as aluminum oxide and zinc oxide.

Pseudoamphoteric compounds are either structurally related to true amphoteric compounds or capabl of inducing the same function when they are incorporated into the compositions containing alpha hydroxyacids or ketoacids. Some examples of pseudoamphoteric compounds are creatinine, stearamidoethyl diethylamine, stearamidoethyl diethanolamine, stearamidopropyl dimethylamine, quaternary ammonium hydroxide and quaternium hydroxide.

The amphoteric composition of the instant invention contains in combination an alpha hydroxyacid or alpha ketoacid and an amphoteric or pseudoamphoteric compound. There are two advantages of utilizing an amphoteric or the like compound in the therapeutic composition containing an alpha hydroxy or ketoacid. These are (a) the overall pH of the composition is raised, so that the composition becomes less or non-irritating to the skin and (b) some alpha hydroxy or ketoacid molecules react with the amphoteric compound to form a quadruple ionic complex which acts as buffering system to control the releas of alpha hydroxy or ketoacid into the skin, therefore, eliminating the skin irritation and still retaining th therapeutic efficaci s.

The following are some examples. 2-Hydroxyethanoic acid (glycolic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.0 and 3.2 when arginine 0.5 M and creatinin 0.5 M respectiv ly are incorporated into the formulations. 2-Hydroxypropanoic acid (lactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.1 and 6.9 when arginine 0.5 M and 1.0 M respectively are

incorporated into the formulations. 2-Methyl 2-hydroxypropanoic acid (methyllactic acid) 1 M aqueous solution has pH 1.9. The pHs of compositions change to 3.3, 3.4 and 3.2 when 0.5 M each of arginin , creatinine and 4-aminobutanoic acid respectively are incorporated into the formulations. 2-Hydroxybutane-1,4-dioic acid (malic acid) 1 M aqueous solution has pH 1.8, but the pH of the composition changes to 3.0 when creatinine 0.5 M is incorporat d into the formulation.

Ideally, an amphoteric compound should contain both anionic and cationic groups or functional groups capable of behaving both as an acid and a base. Although inorganic amphoteric compounds such as aluminum oxide, aluminum hydroxide and zinc oxide may be utilized, organic amphoteric compounds have been found to be more efficient in formulating therapeutic compositions of the instant invention.

Organic amphoteric and pseudoamphoteric compounds may be classified into three groups, namely (a) amino acid type, (b) imidazoline and lecithin amphoterics and (c) pseudoamphoterics and miscellaneous amphoterics.

(a) Amino acid type amphoterics. Amphoteric compounds of amino acid type include all the amino acids, dipeptides, polypeptides, proteins and the like which contain at least one of the basic groups such as amino, imino, guanido, imidazolino and imidazolyl, and one of the acidic groups such as carboxylic, sulfonic, sulfinic and sulfate.

Glycine is a simple amphoteric compound which contains only one amino group and one carboxylic group. Lysine contains two amino groups and one carboxylic group. Aspartic acid contains one amino group and two carboxylic groups. Arginine contains one amino group, one guanido group and one carboxylic group. Histidine contains one amino group, one imidazolyl group and one carboxylic group. Taurine contains one amino group and one sulfonic group. Cysteine sulfinic acid contains one amino group, on carboxylic group and one sulfinic group. The amino group of an amphoteric compound may also be substituted, such as in betaine which is a glycine N,N,N-trimethyl inner salt.

Glycylglycine is a simple dipeptide which contains one free amino group and one free carboxylic group. Glycylhistidine is also a dipeptide which contains one free amino group, one imidazolyl group and one free carboxylic group.

The representative amphoteric compounds of amino acid type may be listed as follows: Glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline and proline.

The related amino acids include homocysteine, homocystine, homoserine, ornithine, citrulline, creatine, 3-aminopropanoic acid, theanine, 2-aminobutanoic acid, 4-aminobutanoic acid, 2-amino-2-methylpropanoic acid, 2-methyl-3-aminopropanoic acid, 2,6-diaminopimelic acid, 2-amino-3-phenylbutanoic acid, phenylglycine, canavanine, canaline, 4-hydroxyarginine, 4-hydroxyornithine, homoarginine, 4-hydroxyhomoarginine, β-lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid, 2-methylserine, 3-phenylserine and betaine.

Sulfur-containing amino acids include taurine, cysteinesulfinic acid, methionine sulfoxide and methionine sulfone.

The halogen-containing amino acids include 3,5-diiodotyrosine, thyroxine and monoiodotyrosine. The imino type acids include pipecolic acid, 4-aminopipecolic acid and 4-methylproline.

The dipeptides include for example, glycylglycine, carnosine, anserine, ophidine, homocarnosine, β-alanyllysine, β-alanylarginine. The tripeptides include for example, glutathione, ophthalmic acid and norophthalmic acid. Short-chain polypeptides of animal, plant and bacterial origin containing up to 100 amino acid residues include bradykinin and glucagon. The preferred proteins include for example protamines, histones and other lysine and arginine rich proteins.

(b) Imidazoline and lecithin amphoterics. The amphoteric compounds of imidazoline derived type are commercially synthesized from 2-substituted-2-imidazolines obtained by reacting a fatty acid with an aminoethylethanolamine. These amphoterics include cocoamphoglycine, cocoamphopropionate, and cocoamphopropylsulfonate. The amphoteric compounds of lecithin and related type include for example, phosphatidyl ethanolamine, phosphatidyl serine and sphingomyelin.

(c) Pseudoamphoterics and miscellaneous amphoterics. Many pseudoamphoteric compounds are chemically related or derived from true amphoterics. For example, creatinine is derived from creatine. Other pseudoamphoteric compounds may include fatty amide amines such as stearamidoethyl diethylamine, stearamidoethyl diethanolamine and stearamidopropyl dimethylamine. Oth r pseudoamphoteric related compounds include quaternary ammonium hydroxide and quaternium hydroxide.

In accordance with the present invention, the alpha hydroxyacid, the alpha ketoacids and th related compounds which are incorporated into amphoteric or pseudoamphoteric compositions for cosm tic conditions and dermatologic disorders may be classified into three groups.

The first group is organic carboxylic acids in which one hydroxyl group is attached to the alpha carbon

of the acids. Th generic structure of such alpha hydroxyacids may be represented as follows:
(Ra) (Rb) C (OH) COOH
where Ra and Rb are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isom ric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra and Rb may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha hydroxyacids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. The alpha hydroxyacids may exist as stereoisomers as D, L, and DL forms when Ra and Rb are not identical.

Typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc. The alpha hydroxyacids of the first group may be divided into (1) alkyl alpha hydroxyacids, (2) aralkyl and aryl alpha hydroxyacids, (3) polyhydroxy alpha hydroxyacids, and (4) polycarboxylic alpha hydroxyacids. The following are representative alpha hydroxyacids in each subgroup.

(1) Alkyl Alpha Hydroxyacids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid)
(H) (H) C (OH) COOH
2. 2-Hydroxypropanoic acid (Lactic acid)
(CH_3) (H) C (OH) COOH
3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid)
(CH_3) (CH_3) C (OH) COOH
4. 2-Hydroxybutanoic acid
(C_2H_5) (H) C (OH) COOH
5. 2-Hydroxypentanoic acid
(C_3H_7) (H) C (OH) COOH
6. 2-Hydroxyhexanoic acid
(C_4H_9) (H) C (OH) COOH
7. 2-Hydroxyheptanoic acid
(C_5H_{11} (H) C (OH) COOH
8. 2-Hydroxyoctanoic acid
(C_6H_{13}) (H) C (OH) COOH
9. 2-Hydroxynonanoic acid
(C_7H_{15}) (H) C (OH) COOH
10. 2-Hydroxydecanoic acid
C_8H_{17}) (H) C (OH) COOH
11. 2-Hydroxyundecanoic acid
(C_9H_{19}) (H) C (OH) COOH
12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid)
($C_{10}H_{21}$) (H) C (OH) COOH
13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid)
($C_{12}H_{25}$) (H) C (OH) COOH
14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid)
$C_{14}H_{29}$) (H) C (OH) COOH
15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid)
($C_{16}H_{34}$) (H) C (OH) COOH
16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid)
($C_{18}H_{37}$) (H) C (OH) COOH

(2) Aralkyl And Aryl Alpha Hydroxyacids

1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid)
(C_6H_5) (H) C (OH) COOH
2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzilic acid)
(C_6H_5) (C_6H_5) C (OH) COOH
3. 3-Phenyl 2-hydroxypropanoic acid (Phenyllactic acid)
($C_6H_5CH_2$) (H) C (OH) COOH
4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid

(Atrolactic acid)
(C_6H_5) (CH_3) C (OH) COOH
5. 2-(4′-Hydroxyphenyl) 2-hydroxyethanoic acid
(4-Hydroxymandelic acid)
(HO-C_6H_4) (H) C (OH) COOH
6. 2-(4′-Chlorophenyl) 2-hydroxyethanoic acid
(4-Chloromandelic acid)
(Cl-C_6H_4) (H) C (OH) COOH
7. 2-(3′-Hydroxy-4′-methoxyphenyl) 2-hydroxyethanoic acid
(3-Hydroxy-4-methoxymandelic acid)
(HO-,CH_3O-C_6H_3) (H) C (OH) COOH
8. 2-(4′-Hydroxy-3′-methoxyphenyl) 2-hydroxyethanoic acid
(4-Hydroxy-3-methoxymandelic acid)
(HO-,CH_3O-C_6H_3) (H) C (OH) COOH
9. 3-(2′-Hydroxyphenyl) 2-hydroxypropanoic acid
[3-(2′-Hydroxyphenyl) lactic acid]
HO-C_6H_4-CH_2(H) C (OH) COOH
10. 3-(4′-Hydroxyphenyl) 2-hydroxypropanoic acid
[3-(4′-Hydroxyphenyl) lactic acid]
HO-C_6H_4-CH_2 (H) C (OH) COOH
11. 2-(3′,4′-Dihydroxyphenyl) 2-hydroxyethanoic acid
(3,4-Dihydroxymandelic acid)
HO-,HO-C_6H_3 (H) C (OH) COOH

(3) Polyhydroxy Alpha Hydroxyacids

1. 2,3-Dihydroxypropanoic acid (Glyceric acid)
($HOCH_2$) (H) C (OH) COOH
2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid)
$HOCH_2$ (HO)CH_2 (H) C (OH) COOH
3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinoic acid, xylonic acid, lyxonic acid)
$HOCH_2$ (HO)CH_2 (HO)CH_2 (H) C (OH) CQOH
4. 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid)
$HOCH_2$ (HO)CH_2 (HO)CH_2 (HO)CH_2 (H) C (OH) COOH
5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.)
$HOCH_2$ (HO)CH_2 (HO)CH_2 (HO)CH_2 (HO)CH_2 (H) C (OH) COOH

(4) Polycarboxylic Alpha Hydroxyacids

1. 2-Hydroxypropane-1,3-dioic acid (Tartronic acid)
HOOC (H) C (OH) COOH
2. 2-Hydroxybutane-1,4-dioic acid (Malic acid)
HOOC CH_2 (H) C (OH) COOH
3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid)
HOOC (HO)CH (H) C (OH) COOH
4. 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid)
HOOC CH_2 C (OH)(COOH) CH_2 COOH
5. 2, 3, 4, 5-Tetrahydroxyhexane- 1, 6-dioic acid (Isomers; saccharic acid, mucic acid etc.)
HOOC $(CHOH)_4$ COOH

(5) Lactone Forms

The typical lactone forms are gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannonolactone, and galactoh ptonolactone.

Th second group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders, is organic carboxylic acids in which the

alpha carbon of the acids is in keto form. The generic structure of such alpha ketoacids may be r presented as follows:

(Ra) CO COO(Rb)

wher in Ra and Rb are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition Ra may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc.

In contrast to alpha hydroxyacids the ester form of alpha ketoacids has been found to be therapeutically effective for cosmetic and dermatologic conditions and disorders. For example, while ethyl lactate has a minimal effect, ethyl pyruvate is therapeutically very effective. Although the real mechanism for such difference is not known, we have speculated that the ester form of an alpha ketoacid is chemically and/or biochemically very reactive, and a free acid form of the alpha ketoacid is released in the skin after the topical application.

The representative alpha ketoacids and their esters which may be useful in amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders are listed below:

1. 2-Ketoethanoic acid (Glyoxylic acid)
(H) CO COOH
2. Methyl 2-ketoethanoate
(H) CO $COOCH_3$
3. 2-Ketopropanoic acid (Pyruvic acid)
CH_3 CO COOH
4. Methyl 2-ketopropanoate (Methyl pyruvate)
CH_3 CO $COOCH_3$
5. Ethyl 2-ketopropanoate (Ethyl pyruvate)
CH_3 CO $COOC_2H_5$
6. Propyl 2-ketopropanoate (Propyl pyruvate)
CH_3 CO $COOC_3H_7$
7. 2-Phenyl-2-ketoethanoic acid (Benzoylformic acid)
C_6H_5 CO COOH
8. Methyl 2-phenyl-2-ketoethanoate (Methyl benzoylformate)
C_6H_5 CO $COOCH_3$
9. Ethyl 2-phenyl-2-ketoethanoate (Ethyl benzoylformate)
C_6H_5 CO $COOC_2H_5$
10. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid)
$C_6H_5CH_2$ CO COOH
11. Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate)
$C_6H_5CH_2$ CO $COOCH_3$
12. Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate)
$C_6H_5CH_2$ CO $COOC_2H_5$
13. 2-Ketobutanoic acid
C_2H_5 CO COOH
14. 2-Ketopentanoic acid
C_3H_7 CO COOH
15. 2-Ketohexanoic acid
C_4H_9 CO COOH
16. 2-Ketoheptanoic acid
C_5H_{11} CO COOH
17. 2 Ketooctanoic acid
C_6H_{13} CO COOH
18. 2-Ketododecanoic acid
$C_{10}H_{21}$ CO COOH
19. Methyl 2-ketooctanoate
C_6H_{13} CO $COOCH_3$

The third group of compounds which may be incorporated into amphoteric or ps udoamphoteric compositions for cosmetic and d rmatologic conditions and disorders, is ch mically related to alpha hydroxyacids or alpha ketoacids, and can be represented by their names instead of the above two gen ric

structures. The third group of compounds include ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebronic acid, citramalic acid, agaricic acid, 2-hydroxyn rvonic acid, aleuritic acid and pantoic acid.

II. Dimeric and Polymeric Forms of Hydroxyacids

When two or more molecules of hydroxycarboxylic acids either identical or non-identical compounds are reacted chemically to each other, dimeric or polymeric compounds will be formed. Such dimeric and polymeric compounds may be classified into three groups, namely (a) acyclic ester, (b) cyclic ester and (c) miscellaneous dimer and polymer.

(a) Acyclic ester. The acyclic ester of a hydroxycarboxylic acid may be a dimer or a polymer. Th dimer is formed from two molecules of a hydroxycarboxylic acid by reacting the carboxyl group of one molecule with the hydroxy group of a second molecule. For example, glycolyl glycollate is formed from two molecules of glycolic acid by eliminating one mole of water molecule. Likewise, lactyl lactate is formed from two molecules of lactic acid. When two molecules of different hydroxycarboxylic acids are intermolecularly reacted, a different dimer is formed. For example, glycolyl lactate is formed by reacting the carboxyl group of lactic acid with the hydroxy group of glycolic acid. The polymer is formed in a similar manner but from more than two molecules of a hydroxycarboxylic acid. For example, glycoly glycoly glycollate is formed from three molecules of glycolic acid. Copolymer is formed from two or more than two different kinds of hydroxycarboxylic acids. For example, glycolyl lactyl glycollate is formed from two molecules of glycolic acid and one molecule of lactic acid.

The acyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

H [-O-C(Ra)(Rb)-CO-]n OH

wherein Ra,Rb = H, alkyl, aralkyl ar aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n = 1 or any numerical number, with a preferred number of up to 200. Ra and Rb in monomer unit 2, 3, 4 and so on may be the same or the different groups from that in monomer unit 1. For example, Ra,Rb = H in monomer unit 1, and Ra = CH_3,Rb = H in monomer unit 2 when n = 2 is a dimer called lactyl glycollate, because the first monomer is glycollate unit and the second monomer is lactic acid unit. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon at ms. The dimer and polymer of a hydroxycarboxylic acid may be present as a free acid, ester or salt form with organic base or inorganic alkali.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative acyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolyl glycollate (Glycolic acid glycollate)
Ra,Rb = H in units 1 & 2, n = 2
2. Lactyl lactate (Lactic acid lactate)
Ra = CH_3,Rb = H in units 1&2, n = 2
3. Mandelyl mandellate
Ra = C_6H_5,Rb = H in units 1 & 2, n = 2
4. Atrolactyl atrolactate
Ra = C_6H_5,Rb = CH_3 in units 1 & 2, n = 2
5. Phenyllactyl phenyllactate
Ra = $C_6H_5CH_2$, Rb = H, in units 1 & 2, n = 2
6. Benzilyl benzillate
Ra,Rb = C_6H_5 in units 1 & 2, n = 2
7. Glycolyl lactate
Ra = CH_3 in unit 1, Ra = H in unit 2, Rb = H in units 1 & 2, n = 2
8. Lactyl glycollate
Ra = H in unit 1, Ra = CH_3 in unit 2, Rb = H in units 1 & 2, n = 2
9. Glycolyl glycolyl glycollate
Ra,Rb = H in units 1, 2 & 3, n = 3
10. Lactyl lactyl lactate
Ra = CH_3, Rb = H in units 1, 2 & 3, n = 3

11. Lactyl glycolyl lactate
Ra = CH_3 in units 1 & 3, Ra = H in unit 2, Ra = H in units 1, 2 & 3, n = 3
12. Glycolyl glycolyl glycolyl glycollate
Ra,Rb = H in units 1, 2, 3 & 4, n = 4
13. Lactyl lactyl lactyl lactate
Ra = CH_3, Rb = H in units 1, 2, 3 & 4, n = 4
14. Glycolyl lactyl glycolyl lactyl glycollate
Ra = H in units 1, 3 & 5, Ra = CH_3 in units 2 & 4, Rb = H in units 1, 2, 3, 4 & 5, n = 5
15. Polyglycolic acid and polylactic acid

(b) Cyclic ester. The cyclic ester of a hydroxycarboxylic acid may also be a dimer or polymer, the most common type however, is a dimer form. The cyclic dimer may be formed from an identical monomer or different monomers. For example, glycolide is formed from two molecules of glycolic acid by removing two molecules of water, and lactide is formed from two molecules of lactic acid in the same manner. The cyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:
[-O-C(Ra)(Rb)-Co-]n
wherein Ra,Rb = H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n = 1 or any numerical number, however with a preferred number of 2. Ra and Rb in units 1, 2, 3 and so on may be the same or the different groups. For example, in glycolide Ra and Rb are H in both units 1 & 2, but in lactoglycolide Ra is H in unit 1, CH_3 in unit 2 and Rb is H in both units 1 & 2. The hydrogen atom in Ra and Rb may be substituted by a halogen atom or a radical such as a lower alkyl, aralkyl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms.

The typical alkyl, aralkyl and aryl groups for Ra and Rb include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative cyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

1. Glycolide
Ra,Rb = H, n = 2 2. Lactide
Ra = CH_3, Rb = H in units 1 & 2, n = 2
3. Mandelide
Ra = C_6H_5, Rb = H in units 1 & 2, n = 2
4. Atrolactide
Ra = C_6H_5, Rb = CH_3 in units 1 & 2, n = 2
5. Phenyllactide
Ra = C_6H_5 CH_2, Rb = H in units 1 & 2, n = 2 6. Benzilide
Ra,Rb = C_6H_5 in units 1 & 2, n = 2
7. Methyllactide
Ra,Rb = CH_3 in units 1 & 2, n = 2
8. Lactoglycolide
Ra = H in unit 1, Ra = CH_3 in unit 2
Rb = H in units 1 & 2, n = 2
9. Glycolactide
Ra = CH_3 in unit 1, Ra = H in unit 2
Rb = H in units 1 & 2, n = 2

(c) Miscellaneous dimer and polymer. This group includes all the dimeric and polymeric forms of hydroxycarboxylic acids, which can not be represented by any one of the above two generic structures, such as those formed from tropic acid, trethocanic acid and aleuritic acid. When a hydroxycarboxylic acid has more than one hydroxy or carboxy group in the molecule a complex polymer may be formed. Such complex polymer may consist of acyclic as well as cyclic structures.

The following hydroxycarboxylic acids have more than one hydroxy groups: glyceric acid, gluconic acid and gluconolactone, galactonic acid and galactonolactone, glucuronic acid and glucuronolactone, ribonic acid and ribonolactone, galacturonic acid and galacturonolactone, ascorbic acid, gulonic acid and gulonolactone, glucoheptonic acid and glucoheptonolactone. These polyhydroxycarboxylic acids can form complex polymers with themselves or with other simple monohydroxymonocarboxylic acids.

The following hydroxycarboxylic acids have more than on carboxyl groups: malic acid, citric acid, citramalic acid, tartronic acid, agaricic acid and isocitric acid. These monohydroxypolycarboxylic acids can also form complex polymers with themselves or with ther simpl hydroxycarboxylic acids.

The following hydroxycarboxylic acids have more than one hydroxy and more than on carboxyl groups: tartaric acid, mucic acid and saccharic acid. These polyhydroxypolycarboxylic acids can form v n

more complex polymers with themselves or with other hydroxycarboxylic acids.

III. Combination Compositions

Any cosmetic and pharmaceutical agents may be incorporated into amphoteric or pseudoamphoteric compositions, or into compositions containing dimeric or polymeric forms of hydroxyacids with or without amphoteric or pseudoamphoteric systems to enhance therapeutic effects of those cosmetic and pharmaceutical agents to improve cosmetic conditions or to alleviate the symptoms of dermatologic disorder. Cosmetic and pharmaceutical agents include those that improve or eradicate age spots, keratoses and wrinkles; analgesics; anesthetics; antiacne agents; antibacterials; antiyeast agents; antifungal agents; antiviral agents; antidandruff agents; antidermatitis agents; antipruritic agents; antiemetics; antimotion sickness agents; antiinflammatory agents; antihyperkeratolytic agents; antidryskin agents; antiperspirants; antipsoriatic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiasthmatic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightning agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical cardiovascular agents and other dermatologicals.

Some examples of cosmetic and pharmaceutical agents are clotrimazole, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzone, rythromycin, tetracycline, clindamycin, meclocycline, hydroquinone, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, betamethasone valerate, betamethason dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate and vitamin E acetate.

IV. Specific Compositions For Skin Disorders

We have discovered that topical formulations or compositions containing specific alpha hydroxyacids or alpha ketoacids, or related compounds are therapeutically very effective for certain skin disorders without utilizing any amphoteric or pseudoamphoteric systems. The alpha hydroxyacids and the related compounds include 2-hydroxyethanoic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid, 2-phenyl 2-methyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid. The alpha ketoacids and their esters include 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate. The mentioned skin disorders include warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

In general, the concentration of the alpha hydroxyacid, the alpha ketoacid or the related compound used in the composition is a full strength to an intermediate strength, therefore the dispensing and the application require special handling and procedures.

If the alpha hdyroxyacid, or the alpha ketoacid or the related compound at full strength (usually 95-100%) is a liquid form at room temperature such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent is directly dispensed as 0.5 to 1 ml aliquots in small vials.

If the alpha hydroxyacid, or the alpha ketoacid or the related compound at full strength is a solid form at room temperature such as 2-hydroxyethanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethanoic acid, 2,2-diphenyl 2-hydroxyethanoic acid and 2-phenyl 3-hydroxypropanoic acid, the solid compound is first dissolved in a minimal amount of vehicle or vehicle system such as water, or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 g, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is used, 0.5 to 3% of for example, hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose or carbomer may be incorporated into the above solution.

To prepare an intermediate str ngth (usually 20-50%), the alpha hydroxyacid, alpha ketoacid or related compound either a liquid or solid form at room temperature is first dissolved in a v hicle or vehicl system such as water, acetone, ethanol, propylene glycol and butan 1,3-diol. For exampl , 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is dissolved in ethanol 56 g and propylen glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

For topical treatment of warts, keratos s, age spots, acne, nail infections, wrinkles or aging related skin changes, patients are advised to apply a small drop of the medication with a toothpick or a fine-caliber,

commonly available artist's camel hair brush to affected lesions only and not surrounding skin. Prescribed applications have been 1 to 6 times daily for keratoses and ordinary warts of the hands, fingers, palms, and soles. For age spots, acne, nail infections, wrinkles and aging related skin changes topical applications have been 1 to 2 times daily.

Very often, frequency and duration of applications have been modified according to clinical respons s and reactions of the lesions and the patient or responsible family member is instructed accordingly. For example, some clinical manifestations other than pain have been used as a signal to interrupt application. These manifestations include distinct blanching of the lesions or distinct peripheral erythema.

Alternatively, an office procedure may be adapted when a full strength of 2-ketopropanoic acid or 70% 2- hydroxyethanoic acid is used for topical treatment of age spots, keratoses, acne, warts or facial wrinkles.

We have found that the above mentioned alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatments of warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

Preparation of the Therapeutic Compositions

Amphoteric and pseudoamphoteric compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, shampoo, spray, stick, powder or other cosmetic and pharmaceutical preparations.

To prepare an amphoteric or pseudoamphoteric composition in solution form at least one of the aforementioned amphoteric or pseudoamphoteric compounds and in combination at least one of the hydroxyacids or the related compounds are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone or other pharmaceutically acceptable vehicle. The concentration of the amphoteric or pseudoamphoteric compound may range from 0.01 to 10 M, the preferred concentration ranges from 0.1 to 3 M. The concentration of hydroxyacids or the related compounds may range from 0.02 to 12 M, the preferred concentration ranges from 0.2 to 5 M.

In the preparation of an amphoteric or pseudoamphoteric composition in lotion, cream or ointment form, at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the relat d compounds are initially dissolved in a solvent such as water, ethanol and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with commonly available cream or ointment bas such as hydrophilic ointment or petrolatum. The concentrations of amphoteric or pseudoamphoteric compounds and hydroxyacids used in the compositions are the same as described above.

Amphoteric and pseudoamphoteric compositions of the instant invention may also be formulated in a gel form. A typical gel composition of the instant invention utilizes at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are dissolved in a mixture of ethanol, water and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

Since dimeric and polymeric forms of hydroxyacids are less stable in the presence of water or the lik vehicle, cosmetic and pharmaceutical compositions should be prepared as anhydrous formulations. Typical vehicles suitable for such formulations include mineral oil, petrolatum, isopropyl myristate, isopropyl palmitate, diisopropyl adipate, octyl palmitate, acetone, squalene, squalane, silicone oils, vegetable oils and the like. Therapeutic compositions containing dimeric or polymeric forms of hydroxyacids do not require any incorporation of an amphoteric or pseudoamphoteric compound. The concentration of the dimeric or polymeric form of a hydroxyacid used in the composition may range from 0.1 to 100%, the preferred concentration ranges from 1 to 40%. Therapeutic compositions may be formulated as anhydrous solution, lotion, ointment, spray, powder or the like.

To prepare a combination composition in a pharmaceutically acceptabl vehicle, a cosmetic or pharmaceutical agent is incorporated into any one of th abov composition by dissolving or mixing th agent into the formulation.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be und rstood that the following xamples are illustrativ and not limited. therefore, any of the aforementioned amphoteric or pseudoamphoteric compounds, hydroxyacids, dimeric or polymeric forms of hydroxyacids may be substi-

tuted according to the teachings of this invention in the following examples.

EXAMPLE 1

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxyethanoic acid (glycolic acid) 7.6 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. An amphoteric composition formulated from 1 M 2-hydroxyethanoic acid and 1 M L-arginine has pH 6.3. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 2

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.3.

≈ 7.3 ok

EXAMPLE 3

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.1.

EXAMPLE 4

A pseudoamphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.2. The composition has pH 4.0 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 5

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxyethanoic acid 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and th solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volum of 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 6

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M dipeptide of β-Ala-L-His for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and L-carnosine (β-alanyl-L-histidine) 11.3 g are dissolved in wat r 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 4.5.

EXAMPLE 7

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M cycloleucine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and 1-aminocyclopentane-1-carboxylic acid (cycloleucine) 6.5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 8

A pseudoamphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.25 M 1,12-diaminododecane for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and 1.12-diaminododecane 5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 4.2.

EXAMPLE 9

An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 5% protamine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and protamine 5 g, isolated and purified from salmon sperm are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 10

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxypropanoic acid (DL-lactic acid) USP grade 9.0 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-arginine has pH 6.9. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 11

An amphoteric composition containing 1M 2-hydroxypropanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volum of 100 ml. The

amphoteric composition thus formulated has pH 3.6. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-lysine has pH 8.4

EXAMPLE 12

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and th solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0

EXAMPLE 13

A pseudoamphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.3. The composition has pH 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 14

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and L-histidine 15.5 g are dissolved in 35 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated as pH 4.9.

EXAMPLE 15

An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxypropanoic acid 9.0 g and glycylglycine 13.2 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 16

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid (methyllactic acid) 10.4 g is dissolved in water 60 ml and propylene glycol 20 ml. L-Arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. An amphoteric composition formulated from 1 M 2-methyl-2-hydroxypropanoic acid and 1 M L-arginin has pH 6.5. The solution has pH 1.9 if no amphoteric compound is incorporated.

EXAMPLE 17

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and 4-aminobutanoic acid 5.2 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 18

An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g and glycylglycine 13.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 19

A pseudoamphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

2-Methyl-2-hydroxypropanoic acid 10.4 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is add d to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4. The composition has pH 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 20

An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid (mandelic acid) 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 5.0. The composition has pH 2.2 if no amphoteric compound is incorporated.

EXAMPLE 21

An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 25 ml of water. The solution thus obtained is mixed with an oil-in-water emulsion to make a total volume of 100 ml. The amphot ric composition thus formulated for pH 4.6.

EXAMPLE 22

A pseudoamphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M cr atinine for cosmetic and d rmatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxy thanoic acid 7.6 g. and creatinine 5.7 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 4.6.

EXAMPLE 23

An amphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M L-citrulline for cosmetic and dermatologic conditions may be formulated as follows.

2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-citrulline 8.8 g are dissolved in water 30 ml, and th solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has pH 3.0.

EXAMPLE 24

An amphoteric composition containing 1 M citric acid and 1 M L-arginine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Citric acid 19.2 g is dissolved in water 50 ml and propylene glycol 10 ml. L-Arginine 17.4 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 25

A pseudoamphoteric composition containing 1 M citric acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

Citric acid 19.2 g and creatinine 11.3 g are dissolved in 40 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has pH 3.7.

EXAMPLE 26

An amphoteric composition containing 1 M malic acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2-Hydroxybutanedioic acid (DL-malic acid) 13.4 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.3. The composition has pH 1.8 if no amphoteric compound is incorporated.

EXAMPLE 27

A pseudoamphoteric composition containing 1 M malic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Malic acid 13.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volum of th solution to 100 ml. The pseudoamphoteric composition thus formulated has pH 3.0. The composition has pH 3.8 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 28

An amphoteric composition containing 1 M tartaric acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

2,3-Dihydroxybutanedioic acid (DL-tartaric acid) 15.9 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. The composition has pH 1.7 if no amphoteric compound is incorporated.

EXAMPLE 29

A pseudoamphoteric composition containing 1 M tartaric acid and 1 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

DL-Tartaric acid 15.0 g and creatinine 11.3 g are dissolved in 35 ml of water. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has pH 3.4.

EXAMPLE 30

An amphoteric composition containing 1 M gluconolactone and 0.5 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and L-arginine 8.7 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1. The composition has pH 5.9 when 1 M instead of 0.5 M L-arginine is incorporated into the formulation. If no amphoteric compound is incorporated the pH of the composition is 1.8.

EXAMPLE 31

An amphoteric composition containing 1 M gluconolactone and 0.5 M 4-aminobutanoic acid for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and 4-aminobutanoic acid 5.2 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals ave been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.2.

EXAMPLE 32

An amphoteric composition containing 1 M gluconolactone and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and glycylglycine 13.2 g are dissolved in water 50 ml and propylene glycol 5 ml. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.1

EXAMPLE 33

A pseudoamphoteric composition containing 1 M gluconolactone and 0.5 M cr atinine for cosmetic conditions and dermatologic disorders may be formulat d as follows.